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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	22

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/668,196	RUSSELL ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11-22,24,26 and 28-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 9, 11-22, 24, 26, and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

1. Claims 1-7, 9, 11-22, 24, 26, 28-33 are pending and under consideration in the present action. The claims were all finally rejected in the action mailed on December 3, 2002. The Applicant submitted a Notice of Appeal on May 19, 2003, and Appeal Briefs on August 19, 2003 traversing the rejections. In view of the Appeal Brief, the Examiner felt it necessary to restate the rejections in the prior action to clarify the record.

As indicated in the prior action, the rejections of record are being maintained in a restated form in which additional references have been added to support the obviousness rejection.

2. The finality of the prior action is being withdrawn , and the present action is being made Non-Final in view of the newly added reference to the obviousness rejections. .

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **(New Rejection)** Claims 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention. These claims read on the use in a method to treat mammals with a cancer with attenuated Measles virus with point mutations in the genome. However, while the claims broadly read on the use of such virus, the Applicant has not provided any examples or guidance as to what point mutations may be made in the viruses such that they retain both their attenuated phenotype, and remain safe and effective for use in the claimed methods.

While the Applicant provides no guidance as to what point mutations may be made, the art indicated that certain mutations in the genome, even in comparison to the attenuated vaccine strains, could lead to viruses with increased pathogenicity. For example, Patterson et al. (J Virol 267(1): 80-9) teaches that certain recombinant viruses, derived from the vaccine Edmonston measles strain, that has increased morbidity when administered in vivo in comparison to the parent vaccine strain. Thus, the art demonstrates that the effect of making mutations in the measles virus genome is unpredictable. Further, it is known in the art of protein mutation generally that the effects of such mutations tend to be unpredictable. See e.g., Bowie et al. Science 247(4948): 1306-10 (teaching that while proteins tend to be tolerant to substitutions, the effect of the substitution on the protein varies with the mutated residues ties role in the protein structure and function- and that, at present, it is not generally possible to predict such roles from sequence alone). In view of this unpredictability in the art, and as the Applicant has not provided any guidance that would lead those in the art to point mutations that result in safe viruses that are also effective in the claimed invention, the Applicant is not enabled the use of any attenuated measles virus comprising any point mutation (or any number of point mutations) in the claimed method of treating cancers.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. **(Prior Rejection-Reformed and Maintained)** Claims 1-7, 9, 11-22, 24, and 28-33 were rejected in the prior actions under 35 U.S.C. 103(a) as obvious over Bateman et al (Cancer Research 60:1492-1497- Bateman et al.) in view of Wiebel et al. (Arch. Dis. Childhood 48:532-536 1973). The rejection of these claims, except claims 18 and 19, is being maintained over the teachings of the Bateman et al. in view of Wiebel, and further in light of the teachings and suggestions of Lindarkis, the Bateman abstract, Taqi, and Bluming, and the teachings of Johnston et al. (J Virol 73(8): 6903-15). The claims have been described in the prior action.

In the Brief, the Applicant has asserted a new ground of traversal and reasserted their traversals of the rejection. The Applicant's arguments in traversal of the rejection may be summarized as follows: 1) the teachings of the prior art follow a different protocol from the claimed method, 2) there is no suggestion in the cited references for the use of an attenuated measles virus to reduce the number of viable cells in a mammal, and 3) the Applicant's invention is non-obvious over the prior art for both demonstrating a surprising result, and satisfying a long felt need in the art. The arguments are not found persuasive.

The protocol used by the Applicant does not adequately distinguish from the prior art.

The Applicant's first argument in traversal of the rejection states "the claimed invention is very different from the prior art." They argue that "killing cells in a dish and treating animals with a transfected tumor cells are vastly different from administering an attenuated measles virus to a mammal to reduce the number of viable cancer cells." However, while the Bateman et al. reference does not teach the administration of attenuated measles virus to a mammal, the teachings of the reference are directed to the use of proteins encoded by viral genes (including the measles virus) to kill tumor cells. See, abstract, and page 1495. The reference also suggests the delivery of the DNA encoding the proteins to the tumor cells in vivo. Page 1497. Thus, while the reference uses different protocols to test the efficacy of the DNAs in treating tumors, these protocols are merely experimental, and not intended to mimic modes of in vivo treatment directly. Rather, by suggesting the delivery of the DNAs to the tumor cells in vivo, the reference is teaching a method with similarity to the claimed methods. While the reference does not teach the administration of attenuated measles virus to tumor cells, the reference does suggest the administration of genes of the measles virus to the cells. Thus, the Applicant's argument that different protocols are used in the reference and the claims is not found persuasive as the reference is suggesting a similar protocol to the claimed methods.

The Applicant also seems to be arguing that a correction to a subtitle and an experimental protocol within the reference is evidence that the reference should not be applied against the claimed invention. However, the correction does not alter any of the suggestions made in the Abstract or the Discussion of the reference. The purpose of the correction is solely to correct the experimental protocols used by the authors in support of their conclusions. It in no way alters the

conclusions that the FMG encoding genes may be used to kill tumor cells in vivo through direct administration of the genes to the cells.

Finally, while it is recognized that the reference does not, alone, suggest the administration of attenuated measles virus to treat tumors, this is not deemed persuasive in overcoming an obviousness rejection based on a combination of references. The Applicant's first argument in traversal is therefore not found persuasive.

The cited references suggest to one or ordinary skill in the art the use of attenuated measles virus to kill tumor cells.

The Applicant next argues the references cited in the actions fail to teach or suggest the use of attenuated measles virus to treat mammalian tumors. The Applicant is correct in that none of the references explicitly indicates that those in the art may reduce the number of tumors in a mammal through the administration of attenuated measles viruses. However, the motivation to combine the knowledge of the prior art need not be explicit in the references cited in support of the rejection. See, MPEP § 2144 (citing numerous decisions by the Federal Circuit and the USPTO Board of Patent Appeals and Interferences in support of this position). Such motivation may also be found, for example, in logic and sound scientific principle. In re Soli, 137 USPQ 797, at 801 (CCPA 1963). Thus, while the Office acknowledges that no one of the cited references states that one in the art may administer an attenuated measles virus to a mammal to reduce the number of cancer cells in the animal, this is not deemed dispositive of whether the art as a whole suggests the claimed invention.

As indicated in the prior actions, and by the Applicant's summary of the reference, Bateman et al. suggests the administration of genes encoding viral fusogenic proteins (FMGs), including those from the measles virus, to cancer cells such that the cells are killed. Weibel teaches that attenuated measles virus may be safely administered to humans. From these two references alone, there may be inadequate motivation to administer the attenuated viruses to humans to kill cancer cells. However, these references are not being considered in a vacuum.

As indicated above, one of ordinary skill in the art would be aware of the teachings of Bateman et al. indicating that the administration of viral (including Measles virus) FMGs is effective to kill tumor cells, and the teachings of Weibel regarding the safety of the attenuated Measles virus. Those in the art would also be aware of the teachings of the Bluming and Taqi references, which indicate that infection by the Measles virus has the side effect of also inducing regression of cancers.

With reference to these two references, the Applicant argues that those in the art reading these references would not be adequately motivated to administer attenuated virus to treat reduce the number of viable cancer cells. Brief, page 9. However, at the time the Applicant filed, those in the art would be faced not only with the separate teachings of Taqi and Bluming, but the these observation s in view of the later teachings regarding Measles virus FMGs. Those in the art are at this point faced with teachings that a specific set of Measles virus gene products are useful to kill cancer cells, and teachings that the whole live virus apparently has the same result. It is also clear from the references that new methods of delivering the genes to cells were desired. See, Linardkis and the Bateman abstract, each suggesting the use of viral vectors to deliver the genes.

From these teachings, it would be obvious to those in the art that the use of the attenuated Measles Viruses would be likely candidates for use in such cancer treatments.

The use of the attenuated virus as convenient vectors for the administration of FMGs to cancer cells is suggested by the additional teachings in the art that wild-type Measles virus infections also induces cancer regression, and that the FMG proteins (the F and H proteins) are necessary for the viral infection of cells. See e.g. Johnston, page 6903 (teaching both the F and H proteins are required for viral cell induced fusion, and that attenuation likely results from modification of proteins controlling other functions that envelope fusion with the target cell). As attenuated virus particles require active fusogenic proteins to be infectious, such particles would be obvious and convenient vectors for the delivery of the FMG genes to cells. Thus, while no one of the references explicitly suggests the use of attenuated Measles virus to treat cancers, or as vectors for the Measles FMG genes, the use of these attenuated particles would have been obvious from the combined teachings of the art.

Those in the art would have had a reasonable expectation of success in the use of the attenuated virus because they would recognize that attenuated viruses that carry the fusogenic proteins required both for the anti-cancer activity and virus infectivity, could be used to deliver the proteins and genes to the target cells. This expectation is further supported by the evidence that live Measles viruses have been shown to have the desired anti-cancer activity. Thus, those in the art would have expected that attenuated virus would cause cancer regression in a manner similar to either the isolated FMG DNAs, or the wild-type Measles virus. The Applicant's argument that the identified references do not suggest the claimed inventions is therefore not found persuasive.

There is insufficient evidence of secondary indicia of non-obviousness to support withdrawal of the rejection.

The Applicant's final traversal is that, even if the references do suggest the claimed invention, the invention is still non-obvious as having achieved unexpected results, and as fulfilling a long felt need in the art. In this argument, the Applicant asserts that two secondary considerations provide further evidence of the nonobviousness of the claimed methods. The Applicant argues first that they achieved an unexpected result in demonstrating that attenuated measles virus resulted in the regression of cancers. The Applicant also argues that the claimed methods satisfy a long felt need in the art by reciting a method for the reduction of viable cancer cells. These arguments are not found persuasive because the Applicant has neither established that it was unexpected that an attenuated Measles virus would have anti-cancer activities, nor established a nexus between the long-felt need for cancer treatments and the presently claimed methods of treating cancers.

With respect to the unexpected results argument, the Applicant has not demonstrated that it was in fact unexpected that the administration of an attenuated Measles virus would result in the regression of cancers. As indicated in the references cited above, it was known in the art both that Measles virus infections had, in several instances, resulted in the regression of cancers. It was also more recently discovered that a particular set of Measles genes and proteins (the FMG genes and proteins) were apparently the source of this anticancer activity. Given that those in the art were aware of these facts, and as it was recognized that the attenuated viruses had active F and H proteins (Johnston, crossover paragraph of pages 6903-04), the fact that the attenuated

virus would have the same anti-cancer activities as the MG compositions and the wild-type virus would not have been unexpected.

The long-felt need argument is likewise flawed. Evidence of long-felt need requires more than an assertion that the Applicant has provided a solution to a general problem in the art. In the present case, while there has been a general and long-felt need for cancer treatments, there has not been a long-felt need for the specific treatment claimed by the Applicant. In addition to the development of several treatments for cancers in the art other than the methods currently claimed, there is also no history of failures by those in the art attempting to use viruses to treat cancer. Rather, there has been a progression in the art using attenuated viruses to treat cancers, and more recently of the use of viral FMGs and experiments with modes of delivery. See e.g., Reichard et al, J Surg Res 52:448-53 (of record in the IDS filed on Jan 5, 2001). Thus, the Applicant has not demonstrated that there was a long-felt need in the art for viral based cancer therapies. Further, as demonstrated by the Bateman references, the use of Measles virus DNA and proteins to treat cancers was already known in the art. Further, the use of FMGs to treat cancers was relatively new in the art. This tends to indicate that the need met by the present invention, that of delivering the FMG compositions to cancer cells, was not a long-felt need, but one that had only recently arisen. The Applicant has therefore not established that there was a long-felt and unsolved need in the art prior to, and solved by, the Applicant's invention.

Dependant Claims

In the Brief, the Applicant argues that the inventions of claims 6, 7, 11, 12, 13, 14, 15, 16, 17, 18 and 19, 20, 21, 22, 31, 32, and 33 stand or fall separately. The Applicant argues that the

combination of references cited above does not render the additional teachings of these claims obvious.

Claims 6, 7 further limit the claimed methods by methods of administration of the virus to the mammals being treated. The Applicant argues that the references do not teach these modes of administration of the virus. However, such modes would have obvious to those in the art. The methods of claim 6 of continuously administering the virus to the mammal, and of claim 7, wherein the viruses are administered in pulses, are methods of administration known in the art. It would have been obvious to those in the art to continuously administer the virus until such time as the treatment has been effective. The administration by pulsing (and devices to do so) is acknowledged by the Applicant on page 16-17 as known in the prior art. It is submitted that use of such methods would be obvious to those in the art as routine methods of administration, and as modes of optimization of the treatments.

Claims 11-15, and 33 further limit the claimed methods to embodiments with ranges of effective dosages of the attenuated virus. The Examiner would like to point out that the Applicant has pointed out on page 16 of the specification that is known in the art that the safe doses of Measles virus range from between 10^3 to 10^{12} pfu, and that the dosages of the measles virus administration to treat cancer cells varies from patient to patient. The Examiner is therefore not persuaded by the Applicant's traversal and maintains the rejection of these claims as obvious optimization of the method of treatment.

Claims 16 and 17 read on the claimed methods wherein the attenuated measles virus are administered in combination with attenuated mumps and rubella viruses, or in combination with attenuated rubella viruses. The Applicant argues that the identified references do not teach the

administration of such viruses to treat cancers. Because the references suggest the use of attenuated Measles virus, and teach compositions comprising these viruses that also comprise the other identified viruses, it would have been obvious to those in the art to administer such vaccines to treat cancer as a convenient Measles containing composition.

Claims 18 and 19 read on embodiments wherein the attenuated virus is modified to express a marker polypeptide. The Applicant argues that the cited references do not teach or suggest such a limitation. The Examiner agrees. The rejection as to these two claims is therefore withdrawn.

Claims 20, 21, and 22 further limit the methods to the treatment of general types of cancers. The Applicant argues that the references do not teach the administration of attenuated Measles viruses to treat any of these forms of cancers. However, as the references suggest, as indicated above and in the prior actions, the administration of attenuated Measles virus to treat tumors generally. See e.g., Bateman et al., abstract, teaching the FMGs are useful for the control of tumor growth, without limitation; and the teachings of Taqi and Bluming indicating that the Measles virus proteins would be effective against different types of cancers. The Applicant's traversal is therefore not found persuasive, and the rejection is maintained against these claims.

Claims 31 and 32 further limit the claimed method to embodiments wherein the attenuated measles virus comprises at least one point mutation, or wherein the virus comprises at least point mutation, but no contiguous point mutations. The Applicant argues that the art does not suggest the use of such attenuated measles viruses to treat cancer. However, the art, in suggesting the use of attenuated measles viruses to treat cancer as indicated above, indicates that any attenuated Measles virus may be used, so long and the FMG gene s and proteins are

operative. In view of this, it would have been obvious to those in the art to use any such attenuated Measles virus, including those with point mutations, and those without contiguous point mutations.

7. **(Prior Rejection-Restated and Maintained)** The rejection of claims 1-7, 9, 11-22, 24, 26, and 28-33 was maintained in the prior action over the teachings of Bateman et al. in view of Usonis et al. (Ped Inf Dis J 18:42-48), and further in light of the teachings of Linardkis, the Bateman abstract, Taqi, Bluming, and Johnston. The Applicant traverses this rejection for substantially the same reasons as indicated above with reference to the rejection over Bateman et al. in view of Wiebel, and further in light of the teachings and suggestions of Linardkis, the Bateman abstract, Taqi, Bluming, and Johnston. For the reasons indicated above and in the prior actions, the rejection of claims 1-7, 9, 11-17, 20-22, 24, 26, and 28-33 is maintained over the teachings of Bateman et al. in view of Usonis, and further in light of the teachings and suggestions of Linardkis, the Bateman abstract, Taqi, and Bluming, and Johnston.

8. **(New Rejection)** Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as obvious over the teachings of Bateman et al. in view of either Weibel or Usonis, and in view of either Asada (Cancer 34: 1907-28, of record in the IDS filed on Jan 5, 2001) or Sato et al (Int J Oral Surg 8:205-11, of record in the IDS filed on July 12, 2002) and further in light of the teachings and suggestions of Linardkis, the Bateman abstract, Taqi, Bluming, and Johnston. The claims and the teachings of the references other that Sato and Asada have been described above. As indicated

above, the teachings of Weibel and Usonis teach formulations of combined attenuated Measles, Mumps, and Rubella vaccines. Each of the Sato and Asada references indicate that the Mumps virus also has anticancer activities. From these references, those in the art would be motivated to use a combination of attenuated Measles and Mumps virus. As such a composition is easily available in the form of the known measles, mumps, and rubella vaccines, those in the art would be motivated to use such compositions as a convenient composition for treatment of cancers using the attenuated measles and mumps viruses.

9. **(Prior Rejection-Restated and Maintained)** The rejection of claims 18 and 19 is maintained for the reasons indicated above over the teachings of Bateman et al., in view of either Wiebel or Usonis, further in view of Duprex (J Virol 73: 9568-75), and in light of the teachings of Linardkis, the Bateman abstract, Taqi, Bluming, and Johnston. The rejection of these claims has been traversed for substantially the same reasons as, and is being maintained for the reasons indicated above with respect to, the rejections minus the Duprex reference above.

10. **Prior Rejection-Restated and Maintained)** The rejection of claim 20 is maintained over the teachings of either Galanis et al. (Gene Therapy 6 (Supp 1): S7, abstract 28) or Russell et al. (Proc. Am Assoc Cancer Res 41: 259, abstract 1648) in view of either Wiebel or Usonis, and further in light of the teachings of Linardkis, the Bateman abstract, Taqi, Bluming, and Johnston. This was previously stated as the rejection of claim 20 over the teachings of either Galanis or Russell in view of either of Weibel or Usonis, and further in view of Linardkis, the Bateman abstract, Taqi, and Bluming. The rejection was traversed for substantially the same

reasons as the other rejections above, and is maintained for the reasons described above and in the prior actions.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
November 12, 2003

James C. Housel
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